Responding to the Rising Incidence of Hepatocellular Carcinoma With Targeted Therapy

Su-Pin Choo, MD
Associate Consultant
Department of Medical Oncology
National Cancer Center, Singapore

Alan P. Venook, MD
Professor of Clinical Medicine
Division of Medical Oncology,
University of California, San Francisco

Hepatocellular carcinoma (HCC) has become increasingly important in the United States and much of the developed world, as its incidence has risen significantly over the past decades.[1,2] It also continues to be a clinically challenging disease that merits much concern, as death rates are equivalent to incidence rates, as highlighted by Abou-Alfa et al in this issue of *Gastrointestinal Cancer Research,* in which they discuss this growing epidemic and the current treatment approaches for advanced HCC.[3]

Several factors have contributed to the increase in HCC incidence. While hepatitis B infection remains the main cause of HCC worldwide, the increased incidence of hepatitis C infection in North America has been identified as the predominant reason for the recent increased rate of HCC in that region.[4] This trend is expected to continue even as the spread of new cases of hepatitis C diminishes, because decades pass in most seropositive hepatitis-C patients before cirrhosis, and later HCC, develops.[2] The obesity epidemic and high prevalence of diabetes in the US population, which exacerbate the risk of cirrhosis from nonalcoholic related steatohepatitis (NASH), is also expected to increase further the incidence of HCC in the coming years.[5,6] Thus, this may be just a harbinger of a bigger wave of HCC cases that will emerge in the future.

TREATMENT OPTIONS IN HCC

Being a heterogenous disease with variable underlying etiology, HCC is notoriously difficult to treat. Most patients present at an advanced stage of disease, and the presence of underlying cirrhosis not only complicates the delivery of conventional therapy, but is often in itself the cause of death. Thus, effective treatment for the cancer itself, if possible, would often be insufficient to alter patient outcomes.[7] A variety of prognostic scores have been developed to stratify HCC patients with underlying liver dysfunction by prognosis to account for the importance of both cancer and liver disease, but no uniformly accepted scoring system exists, nor has any system been validated yet that would help guide appropriate therapy.

Until recently, no treatment had shown any significant survival benefit in advanced HCC in any randomized phase III trial, and HCC has often been regarded as a relatively chemotherapy-resistant cancer. With the impressive results of the SHARP (Sorafenib HCC Assessment Randomized Protocol) trial, which demonstrated a 44% survival advantage with the Raf-kinase and vascular endothelial growth factor (VEGF) inhibitor sorafenib over placebo (median overall survival 10.7 vs. 7.9 months, $P = .00058$), a new standard therapy for advanced HCC treatment has emerged.[8] However, one has to be reminded that this study included patients with mostly pristine liver function (95% or more with Child-Pugh A score in both groups) and excellent performance status (mainly ECOG [Eastern Cooperative Oncology Group] 0-1).

Whether we should be giving sorafenib to our patients with poorer liver function or performance status, who represent the majority of the patients we actually see in clinic, remains unanswered. Also of note, most of the patients treated in the SHARP trial were from Europe and did not have underlying HBV or HCV, so it is still not clear whether sorafenib will be equally effective in HCC patients of different ethnic groups with different underlying etiology. Further studies are required and are planned and under way to address these issues.

Other antiangiogenic agents, such as bevacizumab and anti-epidermal growth factor receptor (EGFR) agents have shown modest activity as single agents. In a pilot study, the combination of bevacizumab and erlotinib showed promising activity in HCC patients with 100% of the patients achieving at least stability of disease, and an impressive median overall survival of 19 months.[9] The considered combination of various targeted agents, based on our understanding of their pathways of action, can produce synergism and enhance antitumor activity.

ASSESSING RESPONSE

Abou-Alfa et al also bring up an important point in their review that increasingly arises with the use of targeted agents, especially in HCC—the lack of objective radiologic response parameters with traditional RECIST (Response Evaluation Criteria in Solid Tumors) criteria seen in patients given sorafenib, while conveying survival benefit, suggest that antitumor activity occurs as an effect not manifested as actual tumor shrinkage (eg, necrosis) or that life is extended by a static effect on cancer proliferation or even on cirrhosis of the liver. This poses a challenge in how we measure clinical response in these patients. Functional imaging with [18F] fluorodeoxyglucose positron emission tomography (FDG-PET) scans has not proven reliable in HCC,[10] and imaging has generally been more difficult in HCC because of its variable presentation radiographically and because of the cirrhotic liver background. Looking for a tumor size reduction in these

patients may be a moot issue, and better methods of assessing treatment response in HCC need to be established.

In summary, the results of the SHARP trial have established sorafenib monotherapy as a new reference standard systemic treatment for select, medically fit patients with advanced HCC. Further studies combining sorafenib with other targeted agents, particularly with synergistic agents and other chemotherapy agents, are under way, both in fit patients and also in the more advanced setting. A randomized phase II trial comparing sorafenib plus doxorubicin vs. doxorubicin alone has been completed, and results suggest the combination is superior to doxorubicin alone, which is consistent with a strategy of multiagent therapy.[11]

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.